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Gamma Band Oscillations in the Early Phase of Psychosis: A Systematic Review

Thomas J Reilly[a*], Judith F Nottage[b], Erich Studerus[c], Grazia Rutigliano[d], Andrea I De Micheli[e], Paolo Fusar-Poli[a], Philip McGuire[a].

a. Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AF
b. Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AF
c. Center for Gender Research and Early Detection, University of Basel Psychiatric Clinics, Basel, Switzerland
d. Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, 16 De Crespigny Park, London, SE5 8AF; Department of Clinical and Experimental Medicine, University of Pisa, Italy.
e. Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy

*Corresponding author

Dr Thomas Reilly

thomas.reilly@kcl.ac.uk

T +44 20 7848 5233

F: +44 20 7848 0976

Highlights

- Gamma oscillations are synchronised by parvalbumin positive interneurons
- Gamma band responses to tasks were reduced in psychosis and at risk populations
- Artefacts occurring within the gamma band have not been adequately addressed
- Longitudinal studies with larger sample sizes, addressing sources of bias are needed

Abstract

Abnormal gamma oscillations, measured by electroencephalography (EEG), have been associated with chronic psychotic disorders, but their prevalence in the early phase of psychosis is less clear. We sought to address this issues by systematically reviewing the relevant literature. We searched for EEG studies of gamma band oscillations in subjects at high risk for psychosis and in patients with first episode psychosis. The following measures of gamma oscillations were extracted: resting power, evoked power, induced power, connectivity and peak frequency. Forty-five studies with a total of 3099 participants were included. There were potential sources of bias in the study designs and potential artefacts. Although there were few consistent findings, several studies reported decreased evoked or induced power in both high risk subjects and first episode patients. Studies using larger samples with serial EEG measurements, and designs that minimise artefacts that occur at the gamma frequency may advance work in this area.

Keywords

Psychotic Disorders; Schizophrenia; Neurophysiology; Electroencephalography; Gamma Rhythm; Review, Systematic.

1. Introduction

Gamma oscillations, with a frequency of 30-130Hz, have been proposed as a mechanism linking neural dysfunction to the symptoms of psychosis (McNally and McCarley 2016). These oscillations are generated through the synchronised activation of pyramidal neuronal assemblies in the cerebral cortex (Fries, Nikolic et al. 2007), a process co-ordinated by an inhibition and rebound excitation cycle mediated by the effects of GABAergic, fast spiking interneurons acting on GABA-A receptors (Bartos, Vida et al. 2007). Glutamatergic afferents at NMDA receptors provide excitatory input to these interneurons (Bartos, Vida et al. 2007). Gamma oscillations are well conserved across species (Buzsaki, Logothetis et al. 2013) and are thought to be fundamental for normal cortico-cortical communication, and cognitive functioning (Fries 2009, Roux, Wibral et al. 2012).

There are multiple paradigms that can be used to measure gamma band oscillations. These include the acquisition of data in the resting state, or in the form of evoked (time-locked and phase-locked to a stimulus), or induced (time-locked to a stimulus only) responses (Roach and Mathalon 2008). Stimuli can be presented in a variety of different sensory modalities, but are usually visual or auditory. These may be presented as steady state responses (e.g. click trains), oddball stimuli or via a cognitive task. Several features of gamma band oscillations can be measured including their power (amplitude of the waveform, squared), functional connectivity (such as coherence or phase synchrony), and peak frequency within the gamma band. Various factors can potentially modify gamma band oscillations. Linguistic stimuli presented using native versus non-native language, for example, affect the gamma band response (Kosem and Wassenhove 2017), as does the level of the participant's attention to the stimulus (Bauer, Stenner et al. 2014). For visual tasks, large high contrast grating stimuli tend to produce gamma responses with highest

amplitude (Hermes, Miller et al. 2015). Additionally, multiple pharmacological agents can affect gamma oscillations, including antipsychotics (Alegre, Molero et al. 2017), stimulants (Berke 2009), ketamine (Vlisides, Bel-Bahar et al. 2017), and cannabinoids (Nottage, Stone et al. 2015).

In post mortem studies of schizophrenia, decreased levels of glutamic acid decarboxylase (crucial for GABA synthesis) have been observed in parvalbumin-positive basket cells (Lewis 2014), a class of GABAergic interneurons that play a major role in the production of gamma oscillations (Buzsaki and Wang 2012). It has been suggested that dysfunction of parvalbumin-positive interneurons, via hypofunction of the NMDA receptor leads to abnormal gamma band oscillations in schizophrenia (Gonzalez-Burgos, Cho et al. 2015), illustrated diagrammatically in Figure 1. Dysfunction of this rhythmic activity has thus been suggested as a mechanism for how abnormal neural circuits could lead to the widespread impairments in cognitive function that are seen in patients with schizophrenia (Lesh, Niendam et al. 2011). There have been multiple reports of abnormal gamma oscillations in patients with chronic schizophrenia (Rutter, Carver et al. 2009, Grutzner, Wibral et al. 2013, Chen, Stanford et al. 2014, Hirano, Oribe et al. 2015). The extent to which these findings are related to illness chronicity or the effects of long term treatment with antipsychotic medication are unclear. These issues can be addressed by studying gamma band abnormalities in subjects who have recently developed a first episode of psychosis, and have received relatively little treatment.

It is possible that changes in gamma band oscillations reflect pathophysiological changes that are associated with the development of psychosis, and may therefore be evident in subjects who are at high risk for the disorder. The assessment of gamma band oscillations in individuals who are at high risk but have not yet

developed a psychotic disorder provides an opportunity to prospectively examine their role in the onset of illness. People who meet criteria for the Clinical High Risk (CHR) state typically present with attenuated psychotic symptoms in the context of a functional decline, and up to 30% of this group will develop a first episode of psychosis within two years (Fusar-Poli, Bonoldi et al. 2012). People with a first degree relative who has a psychotic illness, such as schizophrenia, are also at increased risk of the disorder; with a risk that is 8-10 times greater than that in the general population, but over their entire lifetime, as opposed to the next two years (O'Donovan, Craddock et al. 2009). As they do not have a psychotic disorder but share genetic susceptibility with those who do, subjects at familial high risk may provide endophenotypes, measures of inherited vulnerability (Gottesman and Gould 2003). A third group at increased risk of psychosis are people with schizotypy, personality traits that are qualitatively similar to some features of schizophrenia. These traits are thought to reflect an underlying liability for psychosis (Debbane and Barrantes-Vidal 2015), though the relationship between schizotypal traits and the risk of subsequently developing psychosis is unclear, with large variations in incidence (Debbane, Eliez et al. 2015).

The aim of this review is to critically evaluate the evidence for gamma band abnormalities in the early phase of psychosis. Due to the wide variety in the methods that have been used to measure gamma band oscillations in the literature, we adopted a broad approach: we included all studies quantifying any features of these oscillations in subjects at increased risk for psychosis (CHR, familial risk and schizotypy) or patients with first episode psychosis. We extracted differences in gamma power, frequency and connectivity between these groups and healthy controls.

2. Methods

2.1. Search Criteria

We searched the following databases, from inception to January 2017: MEDLINE, EMBASE, PsychINFO. The following combination of search terms was used: EEG AND ((psychosis OR psychotic OR schizophrenia) AND (risk OR prodrom* OR predict OR first episode)) OR schizotypy). Additionally, references of selected studies were manually searched. The search was performed independently by two investigators (TR and ADM). We first examined study titles and abstracts, obtaining full text articles for all studies which were potentially relevant before deciding whether to include.

2.2 Selection Criteria

We included original research, in English language only, which used human subjects. Studies were included if they reported measures of oscillations within the gamma band (30-130 Hz) using EEG. We included the following populations:

- First episode psychosis, which could include schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder not otherwise specified, bipolar affective disorder with psychotic symptoms or depressive disorder with psychotic symptoms, based on either ICD-10 or DSM criteria. 'First episode' was based on the study author's own definition, which could include, for example, patients undergoing their first hospitalisation for psychosis, or psychotic symptoms presenting for the first time in the past 24 months.
- CHR for psychosis, defined using diagnostic criteria based on a valid clinical tool such as Criteria for Prodromal Syndrome, Basel Screening Instrument for Psychosis, or Structured Interview for Prodromal Syndrome.

- Familial risk, defined as having a first degree relative with a diagnosis of schizophrenia or schizoaffective disorder.
- Schizotypy, defined as populations with measures of schizotypy (such as the Schizotypal Personality Disorder Questionnaire), or those with schizotypal personality disorder based on DSM or ICD-10 criteria.

We excluded reviews, conference abstracts, animal studies, studies using only MEG and studies which measured Event Related Potentials (ERPs) or oscillations outwith the gamma band. We excluded studies of participants with psychotic disorders who were not in their first episode or first hospitalisation. We made no restriction as to what aspect of gamma oscillations were measured and therefore included studies reporting resting, induced and evoked power, functional connectivity and peak gamma frequency. We included overlapping data-sets if they measured different aspects of gamma oscillations.

2.3 Data Extraction

We recorded the following variables from each article: author, year of publication, study population, task used to produce gamma oscillations and quality of each study. We also extracted all measures of gamma oscillations: resting power, evoked power, induced power, functional connectivity and peak frequency. We recorded whether subjects experiencing their first episode of psychosis were exposed to antipsychotic medication. This was done by two authors (TR and ADM), with disagreement resolved by discussion. Effect sizes in the form of Hedge's g were calculated where possible to correct for bias from small sample sizes.

2.4 Assessment of Bias

We assessed risk of bias using a modified version of the Newcastle-Ottawa scale (see Appendix) for the evaluation of non-randomised studies (Stang 2010). The scale evaluates the quality of reporting. According to this tool, every study is judged on three broad categories: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest. We adapted this scale by rating selection of cases as 1 if a validated diagnostic instrument was used and 0 if not. We also rated ascertainment of gamma 1 if this was done blindly in regard to case-control status and 0 if not. In total, a study could score between 0-9, from lowest to highest quality. We also recorded whether the following gamma artefacts had been addressed: power line noise, muscle artefact and saccadic artefact. This was scored from 0-3; we did not score artefact removal which was done by a voltage threshold or manually through visual inspection.

3. Results

45 studies were included, see PRISMA flow-chart Figure 2, comprising a total of 3099 participants. Of these, 42 were independent datasets, as there were 3 pairs of overlapping samples (Kikuchi, Koenig et al. 2007, and Kikuchi, Hashimoto et al. 2011, Tcheslavski 2008, and Tcheslavski and Beex 2010, Ramyead, Kometer et al. 2015, and Ramyead, Studerus et al. 2015). 17 studies included first episode patients, 5 were of CHR, 14 were of people at familial risk, 8 were of schizotypy and one study (Tada, Nagai et al. 2014) included both CHR and first episode patients. The measures of gamma oscillations included are described in Table 1.

3.1 First Episode Psychosis

Studies involving patients with first episode psychosis are shown in Table 2. These comprised a total of 1125 participants; 522 patients and 603 healthy controls. Most patients had a diagnosis of schizophrenia, defined by DSM-IV criteria in 11 studies

(Gallinat, Winterer et al. 2004, Yeragani, Cashmere et al. 2006, Kikuchi, Koenig et al. 2007, Flynn, Alexander et al. 2008, Spencer, Salisbury et al. 2008, Williams, Whitford et al. 2009a, Williams, Whitford et al. 2009b, Minzenberg, Firl et al. 2010, Kikuchi, Hashimoto et al. 2011, Taylor, McCarley et al. 2013, Tada, Nagai et al. 2014), ICD-10 criteria in 3 (Tikka, Yadav et al. 2014, Garakh, Zaytseva et al. 2015, Ramyead, Studerus et al. 2016), and a composite of these in 4 (Slewa-Younan, Gordon et al. 2004, Symond, Harris et al. 2005, Andreou, Nolte et al. 2015, Leicht, Andreou et al. 2015). Five studies were of participants who were naïve to antipsychotic medication (Kikuchi, Koenig et al. 2007, Kikuchi, Hashimoto et al. 2011, Ramyead, Studerus et al. 2016, Tikka, Yadav et al. 2014, Yeragani, Cashmere et al. 2006).

Seven first episode studies utilised resting state paradigms: of these, 4 measured gamma power. Compared with healthy controls, power was increased in one study (Tikka, Yadav et al. 2014), but in 3 there were no significant group differences (Yeragani, Cashmere et al. 2006, Andreou, Nolte et al. 2015, Garakh, Zaytseva et al. 2015). Increased current source density activity in the left medial frontal gyrus was reported in one study (Ramyead, Studerus et al. 2016).

One study (Kikuchi, Koenig et al. 2007) reported that patients showed increased gamma global field synchronisation. Another described decreased mean coherence of spectral power between C4 and F4 electrodes (Yeragani, Cashmere et al. 2006), and a trend for reduced mean phase between C4 and F4. Other studies reported increased orthogonalised power envelope correlation (Andreou, Nolte et al. 2015), and increased omega complexity (Kikuchi, Hashimoto et al. 2011), respectively.

Auditory oddball tasks were used in 6 first episode studies. Evoked power was decreased in one (Taylor, McCarley et al. 2013). In another, there was no overall

difference, although there was a decrease in the right frontal region (Gallinat, Winterer et al. 2004). Four studies measured gamma phase synchrony; 3 (Slewa-Younan, Gordon et al. 2004, Symond, Harris et al. 2005, Williams, Whitford et al. 2009a) showed a decrease in synchrony, while one (Flynn, Alexander et al. 2008) showed an increase. The latency of gamma phase synchrony was found to be increased in the study by Slewa-Younan, Gordon et al. (2004), but decreased in the study by Symond, Harris et al. (2005). Decreased inter-trial phase locking was reported in the study by Taylor, McCarley et al. (2013).

Two first episode studies measured auditory steady state responses. One reported decreased evoked power and phase locking factor in both patients with schizophrenia and patients with affective psychosis (Spencer, Salisbury et al. 2008). The other reported decreased induced power and inter-trial phase coherence in schizophrenia (Tada, Nagai et al. 2014).

An auditory reaction task demonstrated decreased power and phase-locking factor in first episode schizophrenia (Leicht, Andreou et al. 2015). Similarly, induced power was decreased in response to a preparatory cognitive control task, Preparing to Overcome Prepotency (Minzenberg, Firl et al. 2010). Increased phase synchrony in first episode schizophrenia was described in a study of an emotion perception task (Williams, Whitford et al. 2009b).

One study examined gamma synchrony in relation to volumetric MRI data in 13 first episode participants (Williams, Whitford et al. 2009a), reporting that patients showed an inverse relationship between gamma synchrony and grey matter volume in right temporal and parieto-occipital regions.

3.2 Clinical High Risk

Studies of CHR subjects are shown in Table 3. These comprised a total of 370 participants; 229 at risk of psychosis and 141 healthy controls. 3 studies used resting EEG, although 2 of these (Ramyead, Kometer et al. 2015, Ramyead, Studerus et al. 2015) used the same dataset. The first reported an increase in spontaneous power in the medial prefrontal cortex in CHR patients who later developed psychosis, compared with healthy controls. Machine learning was then applied to this dataset in the second study. Predictions of transition were made using current source density in the gamma and beta bands, with an internally cross-validated area under the receiver operating characteristic curve (AUC) of 0.77. By contrast, Andreou, Leicht et al. (2015) found no differences in spontaneous power or resting connectivity in CHR, as quantified by the multivariate interaction measure.

Perez, Roach et al. (2013) used an auditory reaction task was used to measure evoked power, total power and phase locking factor. Evoked power was reduced in CHR subjects, whereas total power showed no difference, and there was a trend for phase locking factor to be decreased (p=0.057). Leicht, Vauth et al. (2016) used an auditory reaction task to investigate gamma power, peak frequency and phase locking factor. Evoked power and peak frequency were decreased, while there was no difference in latency of peak gamma response between groups. Phase locking factor was decreased, though this did not reach statistical significance (p=0.092). Tada, Nagai et al. (2014) used an auditory steady state response paradigm to measure induced power and inter-trial phase coherence, both of which were decreased in the CHR group.

Leicht, Vauth et al. (2016) simultaneously recorded EEG and fMRI while participants performed a cognitively demanding auditory reaction task. Evoked gamma power

peaks were coupled with BOLD signal. There was significantly reduced activation of a network which included bilateral auditory cortices, the thalamus anterior cingulate cortex and dorsolateral prefrontal cortex in the CHR group.

3.3 Familial High Risk

Most of these studies have examined the unaffected relatives of patients with schizophrenia, as shown in Table 4, apart from Hong, Summerfelt et al. (2004) who recruited relatives of patients who also had schizophrenia spectrum personality traits. In total, 1381 participants were included; 640 at familial risk and 741 controls with a negative family history.

Resting EEG was used in 5 studies. Increased spontaneous power was reported by Bandyopadhyaya, Nizamie et al. (2011), and Tikka, Nizamie et al. (2015), but no difference in power was found by Winterer, Egan et al. (2001), Hong, Summerfelt et al. (2012). Venables, Bernat et al. (2009) found no group differences with ‘eyes closed’, but increased spontaneous power in familial high risk subjects with ‘eyes open’. In terms of coherence, Bandyopadhyaya, Nizamie et al. (2011) reported decreased spectral coherence at rest, while Tikka, Nizamie et al. (2015) found no differences in inter or intra hemispheric spectral coherence.

Auditory oddball tasks were used in 4 studies. Increased frontal noise power was reported by Winterer, Coppola et al. (2004), whereas Diez, Suazo et al. (2013) found no difference in gamma noise magnitude. Decreased evoked spectral power was reported in unaffected monozygotic twins of schizophrenia patients (Hall, Taylor et al. 2011a). Phase locking factor was also decreased but did not reach statistical significance. No differences were reported in total spectral power by Diez, Suazo et al. (2014).

Paired auditory clicks were used to examine power, showing decreased evoked power in response to the first stimuli and an increased response to the second stimuli (Hall, Taylor et al. 2011b). However, neither difference was statistically significant. Another paired auditory click paradigm showed no difference in power between groups (Hong, Summerfelt et al. 2012).

Auditory state responses were used by Hong, Summerfelt et al. (2004), and Rass, Forsyth et al. (2012), both showed decreased power in those at familial risk. Decreased phase locking factor was also reported by Rass, Forsyth et al. (2012). An auditory reaction task showed decreased evoked power and decreased phase locking factor in unaffected siblings of schizophrenia patients (Leicht, Karch et al. 2011).

3.4 Schizotypy

Eight studies examined gamma in relation to schizotypy, comprising a total of 223 participants (Table 5). Five studies (Vernon, Haenschel et al. 2005, Tcheslavski 2008, Tcheslavski and Beex 2010, Koychev, Deakin et al. 2011, Fuggetta, Bennett et al. 2014) divided healthy volunteers into two groups based on their scores on a schizotypy scale, 2 (Skosnik, Krishnan et al. 2006, Kornmayer, Leicht et al. 2015) correlated measures of gamma with schizotypy scores of healthy volunteers and one (Brenner, Sporns et al. 2003) compared people with schizotypal personality disorder to healthy controls. The Schizotypy Personality Questionnaire (Raine 1991) was used to measure schizotypy in 7 studies (Vernon, Haenschel et al. 2005, Skosnik, Krishnan et al. 2006, Tcheslavski 2008, Tcheslavski and Beex 2010, Koychev, Deakin et al. 2011, Kornmayer, Leicht et al. 2015), while Fuggetta, Bennett et al. (2014) used the Unusual Experiences and Cognitive Disorganisation sub scales of

the Oxford-Liverpool Inventory of Feelings and Experiences (Mason and Claridge 2006).

In the resting state, Fuggetta, Bennett et al. (2014) reported decreased spontaneous power in subjects with high schizotypy (though this was not statistically significant), while Tcheslavski (2008) reported increased power and Tcheslavski and Beex (2010) reported increased phase synchrony.

There was no difference in evoked power from auditory steady state response in subjects with schizotypal personality disorder compared with healthy controls (Brenner, Sporns et al. 2003). Skosnik, Krishnan et al. (2006) described a negative correlation of schizotypal scores with evoked power using auditory steady state responses, while positive correlation of visually evoked power with schizotypy scores was reported by Kornmayer, Leicht et al. (2015).

Using a visual working memory task, Koychev, Deakin et al. (2011) found that high versus low schizotypy was associated with increased evoked power and decreased phase locking factor in fronto-central and central-occipital regions. Increased evoked power and decreased phase locking factor was seen in high schizotypy compared with low schizotypy in fronto-central and central-occipital regions. Vernon, Haenschel et al. (2005) used an auditory habituation task to show that individuals with high versus low unreality schizotypy scores had decreased spectral power in the central posterior region, but this was not statistically significant.

3.5 Relationship with Psychopathology

Thirteen studies examined the relationship between gamma oscillations and psychopathology; 10 in patients with first episode psychosis, 2 in those at CHR and

one using both groups. Tikka, Nizamie et al. (2015) reported a negative correlation between low gamma power (30-50Hz) in the left temporal region and Positive and Negative Syndrome Scale (PANSS) general psychopathology subscale ($r=0.427$ $p<0.05$); a positive correlation between high gamma power (70-100Hz) in the right occipital region and the PANSS general psychopathology subscale; and a negative correlation between PANSS total scores and left temporal gamma power at both 30-50Hz ($r=0.473$ $p<0.01$) and at 50-70Hz ($r=0.389$ $p<0.05$).

Taylor, McCarley et al. (2013) reported positive correlations of phase locking factor and PANSS total scores at Fz ($r=0.47$ $p=0.024$) and Cz ($r=0.43$ $p=0.004$). They also reported positive correlation of PANSS total scores and power at Fz ($r=0.71$ $p<0.001$) and Cz ($r=0.61$ $p=0.002$). There were trends for positive correlations between power at Fz and PANSS positive subscore ($r=0.39$ $p=0.065$), PANSS hallucinations subscore ($r=0.39$ $p=0.66$) and PANSS thought disorder ($r=0.41$ $p=0.051$). They found no significant correlations between power or phase-locking factor and Scale for the Assessment of Positive Symptoms or Scale for the Assessment of Negative Symptoms.

Williams, Whitford et al. (2009a) reported a negative correlation between change in PANSS reality distortion factor and left temporal synchrony ($r=-0.621$ $p=0.006$), indicating that an improvement in these symptoms was correlated with increased synchrony in this area. Spencer, Salisbury et al. (2008) reported a positive correlation between phase locking and PANSS positive scores ($\rho=0.72$ $p=0.003$) in patients with first episode schizophrenia but did not find correlations in patients with first episode affective psychosis. Tada, Nagai et al. (2014) reported negative correlations between PANSS General scores and both inter trial coherence ($r=-0.73$ $p=0.004$), and event related spectral perturbation ($r=-0.70$ $p=0.008$) in patients with

first episode schizophrenia. They also reported negative correlation of event related spectral perturbation with both PANSS positive scores (r=-0.53 p=0.04) and PANSS general psychopathology scores (r=-0.70 p=0.004) in people at CHR. Garakh, Zaytseva et al. (2015) reported negative correlation of PANNS positive score and power at Fp1 (r=-0.368), in patients with a first episode of schizoaffective disorder.

Leicht, Andreou et al. (2015) reported a negative correlation between PANSS negative scores and both phase locking factor (ρ=-0.510 p=0.05) and evoked power (ρ=-0.600 p=0.02) in patients with first episode schizophrenia. They also reported a trend for correlation between evoked power and the disorganised factor of PANSS (ρ=0.504 p=0.06). Williams, Whitford et al. (2009b) reported positive correlation of absolute synchrony at left temporal region and PANSS negative scores (R^2=0.18) in patients with first episode schizophrenia.

A number of studies found no correlation between symptoms scores and measures of gamma oscillations in patients with first episode psychosis (Gallinat, Winterer et al. 2004, Flynn, Alexander et al. 2008, Kikuchi, Hashimoto et al. 2011) and those at CHR (Perez, Roach et al. 2013, Leicht, Vauth et al. 2016).

3.6 Relationship with Cognition

Tada, Nagai et al. (2014) reported that attentional functioning, measured by the Brief Assessment of Cognition in Schizophrenia, was significantly correlated with both inter trial coherence (r=0.75 p=0.003) and event related spectral perturbation (r=0.76 p=0.003) in patients with first episode schizophrenia. Ramyead, Kometer et al. (2015) reported current source density of gamma oscillations was highly correlated with a scale for measuring abstract reasoning (r=0.734 p<0.001) in people at CHR

who went on to transition to psychosis, but not in those at CHR who did not transition or in healthy controls.

Taylor, McCarley et al. (2013) reported no significant correlations between evoked power or phase locking factor and semantic or working memory measures in patients with first episode schizophrenia. Leicht, Vauth et al. (2016) report no correlation between error rates or reaction time in a cognitively demanding auditory task and gamma band responses.

3.7 Bias

The assessment of bias in each study is reported in Table 5 and the assessment of gamma artefacts in Table 6.

4. Discussion

In this systematic review, we identified 45 studies that examined gamma oscillations using EEG in the early phase of psychosis. The large degree of between-study heterogeneity in the participant population studied, in the stimuli used to evoke or induce gamma responses, and in the method employed to quantify the gamma signal precluded a meta-analysis. Overall, most studies of CHR subjects, familial risk subjects and first episode patients showed decreased evoked and induced power compared with healthy controls. A number of studies also reported increased resting gamma power in these groups, though this was a less consistent finding.

4.1 First Episode Psychosis

The largest group studied comprised patients with first episode psychosis. Decreased gamma power in response to a task was a relatively consistent finding, with 5 out of 6 studies reported reduced evoked or induced power. The only study

which did not find a difference in evoked power overall, reported decreased power in the right frontal region (Gallinat, Winterer et al. 2004). This is consistent with the patterns of deficits in gamma band responses found in chronic schizophrenia (Senkowski and Gallinat 2015). Mouse models suggest that hypofunction of the NMDA receptor on fast spiking parvalbumin positive interneurons underlies this impairment in gamma rhythm induction (Carlen, Meletis et al. 2012).

Spontaneous gamma power was increased in one first episode study, but showed no statistically significant difference in 3 others. This is not in line with the suggestion that schizophrenia is associated with increased resting gamma power (White and Siegel 2016). It is also inconsistent with preclinical and computer models of NMDA receptor hypofunction, which predict increased baseline gamma power and decreased power in response to stimulus (Jadi, Behrens et al. 2016). These discrepancies relate to spontaneous gamma power being selectively increased during auditory steady state stimulation but not at rest, as has been reported in schizophrenia (Hirano, Oribe et al. 2015).

The disconnection hypothesis (Friston, Brown et al. 2016) proposes that schizophrenia is associated with decreased markers of connectivity, such as coherence. Several studies reported that phase locking and phase synchrony in response to tasks were decreased, but others reported increases in omega complexity, global field synchronisation, and orthogonalised power envelope correlation. Measures of functional connectivity, such as coherence or phase synchronisation are particularly difficult to compare between studies, as there is no single optimal method. There are at least 42 different methods that can be used to measure oscillatory interactions, which can produce differing results from the same dataset (Wang, Benar et al. 2014). These must be interpreted cautiously, as issues

such as common inputs, common references, differences in signal-to-noise ratio between channels and volume conduction can all lead to spurious results (Bastos and Schoffelen 2015). Notably, Andreou, Nolte et al. (2015) reported increased gamma band connectivity in first episode schizophrenia measured by orthogonalised power envelope correlation but in an overlapping sample, there was no difference in connectivity as measured by the multivariate interaction measure (Andreou, Leicht et al. 2015). The findings from studies that used EEG to assess functional connectivity in the early phase of psychosis were thus inconclusive.

4.2 High Risk Subjects

The decrease in both evoked and induced power that was evident in several first episode studies was also found in studies of CHR populations; all 3 studies measuring these features showed reductions compared with healthy controls. There was also a suggestion of increased resting gamma power, though this was a solitary report (Ramyead, Kometer et al. 2015). A measure of neural synchrony in the form of inter-trial phase coherence was decreased in CHR subjects (Tada, Nagai et al. 2014), a finding that was also reported in first episode patients.

The familial risk group showed results which were broadly in keeping with those in patients with first episode psychosis. Resting power was either increased or showed no difference between groups, evoked and induced gamma power was reduced in 3 of 4 reports, and phase-locking factor was decreased in all 3 of the studies that reported this measure. As these gamma band abnormalities were present in the unaffected relatives of patients, it suggests they reflect a genetic susceptibility, and thus may represent trait biomarkers of psychosis (Koychev, Barkus et al. 2011).

It was more difficult to interpret the findings from studies of gamma oscillations in people with schizotypy, as they used a variety of different experimental designs, including correlation with schizotypy scores, comparisons between low and high schizotypy individuals, and comparison between schizotypal personality disorders and healthy controls. Furthermore, the results were largely inconsistent across studies.

EEG abnormalities are of particular interest in subjects at CHR for psychosis, as they might be useful in facilitating the prediction of illness onset in a clinical setting. Most studies of CHR subjects to date have involved sample sizes that were too small to permit analysis of the relationship between gamma band measures and later transition to psychosis. Ramyead, Studerus et al. (2015), however, utilised a machine learning approach which incorporated measures of both beta and gamma oscillations from a sample of n=53 to predict which subjects would go on to develop psychosis. They predicted transition to psychosis with an AUC of 0.77. Perez, Roach et al. (2013) did not find differences between CHR subjects who subsequently transitioned and those who did not, in terms of evoked power, total power or phase-locking factor. A key caveat in the interpretation of these findings is that the number of CHR subjects who subsequently developed psychosis in these studies was still small (n=18 and n=15, respectively), so they may have lacked the statistical power to detect significant effects.

Correlations between measures of gamma oscillations and psychotic symptomatology were inconsistent between studies, with both positive and negative correlations, as well as no correlation reported. This is similar to the findings in patients with established schizophrenia, where both positive (Spencer, Niznikiewicz et al. 2009, Suazo, Diez et al. 2012, Hirano, Oribe et al. 2015), negative (Krishnan,

Vohs et al. 2005, Grutzner, Wibral et al. 2013, Spironelli and Angrilli 2015) as well as no correlations (Hamm, Ethridge et al. 2012, Roach, Ford et al. 2013, Tikka, Yadav et al. 2014) have been reported. This apparent discrepancy between studies may be partly explained by the use of differing experimental paradigms and differing aspects of gamma oscillations being measured.

Two studies reported significant correlations of gamma oscillations and cognitive scores: using attentional functioning in first episode schizophrenia, and abstract reasoning in those at CHR who went on to develop psychosis. However, another two found no significant correlations. This contrasts with studies which report abnormal gamma oscillations are associated with poor performance in a number of cognitive tasks in patients with established schizophrenia (Senkowski and Gallinat 2015). Gamma oscillations are also proposed as a key mechanism for working memory in healthy subjects, particularly when coupled with theta oscillations (Lisman and Jensen 2013, Roux and Uhlhaas 2014). Lack of agreement between studies may be attributable to an inconsistency in the measures of cognitive function and in methods of examining gamma oscillations.

4.3 Bias

We assessed each study's risk of bias using an adapted version of the Newcastle-Ottawa scale. However, there are likely more forms of bias which are not detected by this scale. EEG is clearly a versatile investigational technique, whereby multiple measures and analyses can be undertaken in across a range of frequencies. It is conceivable that researchers may carry out multiple tasks and analyses yet only report those which are most favourable. Selective reporting of these outcomes would make a study prone to bias, with more statistically significant outcomes and analyses likely to be included (Ioannidis, Munafo et al. 2014). Unless a study protocol is made

available before the study commences, it is difficult to evaluate whether selective reporting has taken place. We did not find evidence for pre-specified outcomes and analyses in any of the included studies. There is suggestion of selective reporting by Donkers, Schwikert et al. (2011) who state in their methods that phase locking factor, evoked power and total power were compared between relatives and controls in the gamma band but do not report the results of these comparisons. Similarly, EEG uses a number of electrodes on which statistical inferences can be made. Some of the included studies used groups of electrodes in their analyses (Tikka, Yadav et al. 2014), while others reported results for individual electrodes (Diez, Suazo et al. 2014). Not only does this introduce more variability in the reporting of results, it also poses a multiple comparison problem, which no study seemed to account for in their reporting of statistics. The reproducibility of this field could be improved by investigators publishing protocols and analysis plans before conducting research, as well as incentivising replication of previously reported results (Ioannidis, Greenland et al. 2014).

Within the literature examined, there was considerable variability in the way that the definitions of ‘first episode’ of a psychotic disorder were defined, ranging from presentation with psychotic symptoms for the first time, first hospitalisation for psychosis, or psychotic symptoms presenting for the first time in the past 24 months, or no clear definition at all. Most studies contained participants had been exposed to antipsychotic medication, which have been shown to affect gamma band oscillations (Alegre, Molero et al. 2017).

Multiple artefacts can occur within the gamma band, potentially producing spurious results (Nottage and Horder 2015). Power line noise occurs at the frequency of 50 Hz in Europe, which is within the gamma range. It is common to remove a frequency

band containing power line noise, for example with a notch filter. However, this could also remove neuronal gamma signal if it occurs at the same frequency and it may produce spurious oscillations in adjacent frequency bands (Nottage and Horder 2015). Instead, power line noise should be removed by noise cancellation (Nottage, Morrison et al. 2013) or negated by using an electrically shielded room. Electrical activity of extra-ocular muscles associated with blinking is conventionally removed using regression weights calculated from average blink potentials, which are below the gamma frequency (Semlitsch, Anderer et al. 1986). In contrast, orbicularis oculi contraction during blinks occur within the gamma band and as yet, there are no published methods for removing this artefact (Nottage and Horder 2015). Therefore, it can only be reduced by keeping eyes closed or by excluding anterior electrodes from analysis. It has been demonstrated that saccadic eye muscle contraction accounts for previously published induced broad band gamma response 200-300ms after visual stimulus presentation (Yuval-Greenberg and Deouell 2009). This is particularly relevant as people at risk of psychosis have been shown to have increased saccadic eye movements (Gschwandtner, Aston et al. 2003, van Tricht, Nieman et al. 2010). Saccadic muscle potentials can be removed by recording electrical activity at the corner of each eye and subtracting a weighted average of these potentials from the EEG signal (Nottage 2010). A study of muscle paralysis suggests a major component of the gamma signal in published research is actually due to muscle activity of the face, scalp and neck (Whitham, Pope et al. 2007). Prolonged contraction of these muscles may particularly occur at times of stress or emotional arousal (Nottage and Horder 2015). In order to address scalp and neck muscle artefact, EMG should be recorded and removed, through mathematical modelling (Nottage, Morrison et al. 2013). An alternative way of addressing EMG contamination is through independent component analysis (Uriguen and Garcia-

Zapirain 2015), but this method risks rejecting a proportion of genuinely neuronal gamma signal, as well as the artefact (Nottage and Horder 2015).

Of the 45 studies included, only 6 adequately addressed our pre-specified sources of gamma band artefact (Table 7). Even amongst these, independent component analysis was used to remove artefact associated with ocular and facial electrical activity. This method is open to criticism (Nottage and Horder 2015) when correcting for saccades and electromyography. 25 studies did not address any of the potential sources of gamma artefact. A failure to adequately address the multiple non-neuronal artefacts within the gamma range may have resulted in the discrepancy between studies included in this review.

4.4 Sample Size

The sample sizes in most of the studies were small which may have contributed to the inconsistency between studies. The mean sample size was 29 for first episode patients, 38 for CHR subjects, 46 for those at familial risk and 32 for studies of schizotypy. Sample size is a particular issue in studies which seek to link EEG abnormalities in high risk subjects to the subsequent onset of psychosis. Multi-centre studies provide a means of recruiting larger samples, and a number of these are currently ongoing (Addington, Cadenhead et al. 2012). However, the involvement of multiple centres can also introduce site effects, which must be controlled for in the analysis. Travelling subjects undergoing EEG recordings between sites, as well as standardisation of recruitment, presentation of stimuli, and acquisition of data may reduce this variation.

4.5 Further Research Required

This systematic review suggests that gamma oscillations are altered in first episode psychosis and high risk groups, with most evidence for decreased evoked and induced power. However, there were also many inconsistent findings. Although most studies involved auditory stimuli, it is unclear whether this sensory modality is optimal for detecting gamma band abnormalities; visually stimulated gamma responses have also been shown to be abnormal in schizophrenia (Tan, Lana et al. 2013). A further caveat is that the literature to date is almost entirely comprised of cross-sectional studies. Longitudinal studies are required to determine whether gamma abnormalities are a trait or state biomarker of psychosis, whether they pre-date illness onset and whether they can be used clinically to predict outcome.

It would be useful to integrate gamma band findings in the early phase of psychosis with findings from other neuroimaging techniques. However, few EEG studies to date have also collected data from other imaging modalities (Williams, Whitford et al. 2009a, Leicht, Vauth et al. 2016). Since gamma oscillations are thought to be dependent on GABAergic interneurons, combining EEG with imaging techniques that can examine GABA function (such as MRS or PET) would be of particular interest. There is evidence from work in healthy volunteers that visually induced gamma oscillations measured by MEG are related to GABA-A receptor density, measured by the PET tracer flumazenil (Kujala, Jung et al. 2015). However, earlier reports that GABA concentration in the visual cortex measured by MRS predicts peak gamma frequency (Muthukumaraswamy, Edden et al. 2009) were not subsequently replicated (Cousijn, Haegens et al. 2014). The use of EEG in combination with other investigational techniques is of particular interest in the prediction of psychosis in subjects who are at high risk, in whom sequential testing using EEG, MRI and blood biomarkers may substantially improve prognostic accuracy in models in CHR populations (Schmidt, Cappucciati et al. 2017). However, the role of gamma

oscillations as a biomarker for outcomes in psychosis needs further clarification before its clinical utility can be realised

4.6 Limitations

At present, the literature in this area comprises studies that are heterogeneous with respect to the clinical samples, the tasks used to elicit gamma oscillations, the methods used to quantify features of gamma oscillations, the methods used to quantify features of gamma oscillations, and the steps taken to reduce artefacts. This precluded a meta-analysis of the findings, limiting our study to a systematic review. Although we quantified risk of bias using an established tool, there may still have been reporting biases that were less explicit. The amount of data reported by each study was also variable. We calculated effect sizes when the necessary data were available but this was not possible for studies that did not report means, standard deviations, or relevant test statistics. Some studies reported results for each individual EEG electrode used (for example, Diez, Suazo et al. (2013)). Rather than listing each electrode, we chose to report data from the electrodes with the greatest signal, as this was the convention used by most of the other studies that we included.

5. Conclusion

Although at present the literature is too small and heterogeneous to permit a meta-analysis, a systematic review of EEG studies in people at high risk for psychosis and patients with first episode psychosis indicates that decreased evoked and induced gamma band responses are evident in both groups. There is also some evidence that both groups show increased spontaneous power at rest. These findings suggest that EEG measures in the early phase of psychosis have the potential to be used as biomarkers. Studies using larger samples, serial measurements, and designs that

minimise the artefacts that occur at the gamma band frequency may advance work in this area.

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Appendix

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition (diagnosis) adequate?

a) yes, with validated diagnostic instrument (e.g. DSM, ICD, CAARMS, SIPS) ✳

b) yes, e.g. record linkage or clinical diagnosis

c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases ✳

b) potential for selection biases or not stated

3) Selection of Controls

a) community controls (same community as cases) ✳

b) hospital controls or potential for selection bias

c) no description

4) Definition of Controls

a) no history of diagnosis of psychotic disorder, for controls of familial risk, no family history of psychotic disorder ✳

b) no description

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for sex and age ✳

b) study controls for any additional factor ✳

Exposure

1) Ascertainment of gamma

a) ~~secure record (e.g. surgical records)~~ Not applicable

b) neurophysiological analysis where blind to case/control status ✳

c) neurophysiological analysis not blinded to case/control status

d) ~~written self-report or medical record only~~ Not applicable

e) no description

2) Same method of ascertainment for cases and controls

a) yes ✳

b) no

3) Missing data rate

a) same rate for both groups ✳

b) non-respondents described

c) rate different and no designation

Figure Captions

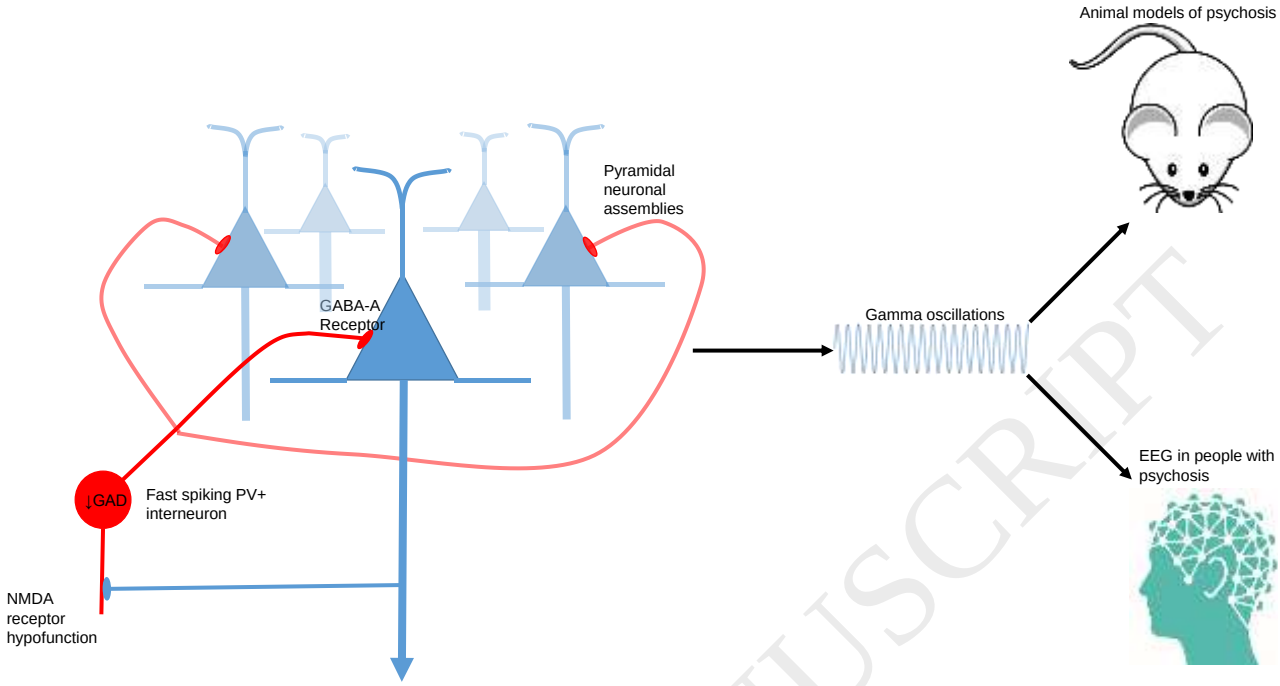

Figure 1
Diagrammatic representation of the production of gamma oscillations. Activation of pyramidal neuronal assemblies, is synchronised by fast-spiking parvalbumin positive GABAergic interneurons. This may be dysfunctional in psychosis through NMDA receptor hypofunction and decreased glutamic acid decarboxylase (GAD). As gamma oscillations are well preserved across species, they can be examined using animal models. They can also be measured directly through EEG.

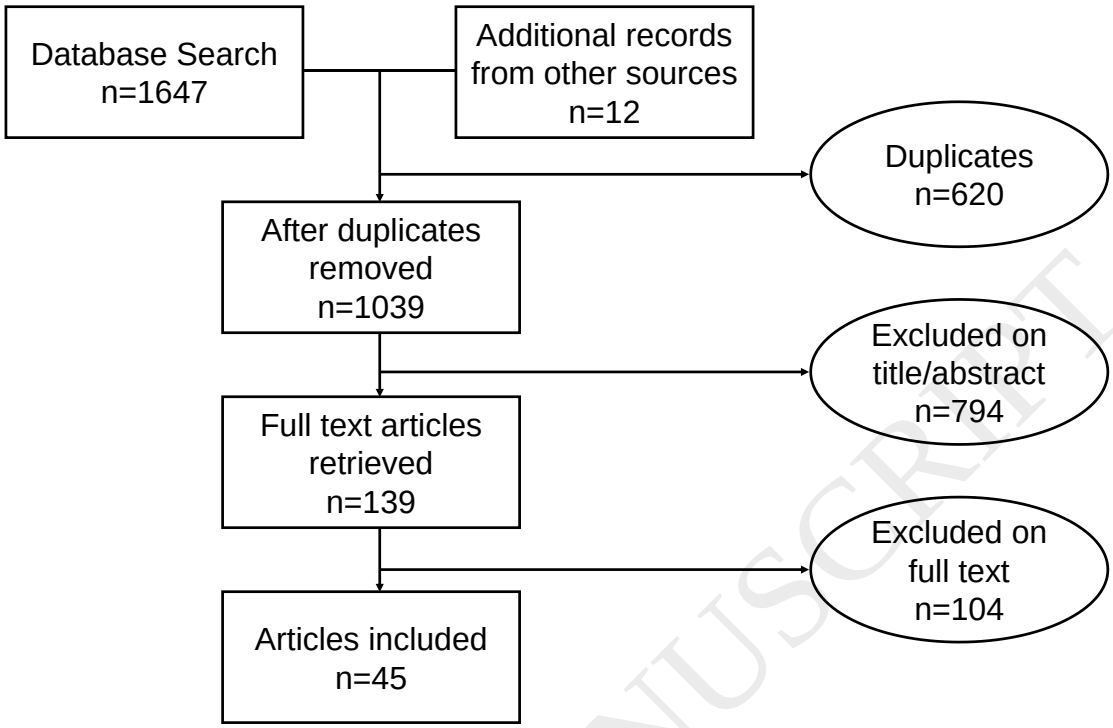

Figure 2
PRISMA flow diagram of included studies.

Tables

Table 1. Measures of Gamma Oscillations Included in this review

Measure	Description
Resting Power	Power is defined as amplitude of the waveform squared. Resting EEG may be recorded with eyes opened or closed.
Evoked Power	Change in power which is time-locked and phase-locked to a stimulus.
Induced Power	Change in power which is time-locked to a stimulus but not phase-locked. Also called event related spectral perturbation.
Total Power	Change in power which contains both phase-locked and non-phase-locked power.
Noise Power	Power not time-locked to stimulus, calculated as the difference between the mean power of single trials and the power magnitude in the averaged potential. Also known as noise magnitude.
Peak Frequency	The frequency with the highest magnitude within the gamma range, measured in Hz.
Global Field Synchronisation	Estimates the relative phase synchrony over all electrodes at a given frequency, calculated by the fraction of total power across electrodes that can be explained by a single phase.
Coherence	Consistency of signal between two channels (various measures of consistency may be used, for example spectral power).
Mean Phase Difference	Difference in the mean angle of the sinusoidal waveform between two channels.
Orthogonalised Power Envelope Correlation	Same-phase signal components are removed (to avoid spurious correlations from the same source) before power estimates and their correlation are calculated.
Omega Complexity	Measure of the global complexity of multi-channel EEG data across the entire scalp, calculated using spatial principal components analysis for all channels.
Inter-Trial Phase Coherence	Degree of phase synchronisation across trials between EEG data and time-locking events. Also called inter-trial phase locking and phase-locking factor.
Phase Synchrony	A singular estimate of the degree of phase-locking across multiple electrodes. Defined as the inverse of circular variance, which is computed from the phase estimate of each electrode, independent from the amplitude.
Current Source Density	A reference-independent measure of the direction, location and intensity of current generators underlying the grossly recorded EEG. Defined as the second spatial derivative of local field potentials.
Multivariate Interaction Measure	Measures the interaction between vector signals based on complex coherence.

Table 2. Gamma Oscillations in First Episode Psychosis

Study	Diagnosis	Diagnostic Tool	Definition of first episode	Patient Number	Control Number	Task	Measurement of Gamma Oscillations	Summary of findings	Direction of difference, compared with controls	Hedge's g
Andreou, Nolte et al. (2015)	Schizophrenia	Mini International Neuropsychiatric Interview	First diagnosis and psychiatric treatment in the past year and presence of psychotic symptoms in any form for no more than five years, 18 receiving antipsychotics.	22	22	Resting, eyes closed	Orthogonalised power envelope correlation	Increased mean functional gamma-band connectivity in the left rolandic operculum of patients compared to controls	↑	N/A
Andreou, Nolte et al. (2015)	Schizophrenia	Mini International Neuropsychiatric Interview	First diagnosis and psychiatric treatment in the past year and presence of psychotic symptoms in any form for no more than five years, 18 receiving antipsychotics	22	22	Resting, eyes closed	Spontaneous power	No difference in gamma power compared with healthy controls	–	-0.038
Garakh, Zaytseva et al. (2015)	Schizophrenia (n=32), Schizoaffective disorder (n=32)	ICD-10	First episode in the acute/subacute phase, recruited on admission to Early Intervention clinic, receiving antipsychotics	64	40	Resting, eyes closed and an arithmetic task	Spectral power at midline, anterior, central and posterior	No statistical difference between first episode schizophrenia, first episode schizoaffective disorder or healthy controls, however mean power for each group not reported	–	N/A
Kikuchi, Hashimoto et al. (2011)	Schizophrenia	DSM-IV	Drug naïve	21	21	Resting, eyes closed	Omega complexity	Increased gamma band omega complexity compared with healthy controls	↑	0.639
Kikuchi, Koenig et al. (2007)	Schizophrenia	DSM-IV	Drug naïve	21	21	Resting, eyes closed	Global field synchronisation (within gamma band (30.5-40.2 Hz))	Increased mean gamma global field synchronisation compared with healthy controls	↑	1.455
Ramyead, Studerus et al. (2016)	Schizophrenia (n=17), Schizoaffective disorder (n=2), Acute polymorphic psychotic disorder (n=7), Schizotypal disorder (n=1)	ICD-10	Drug naïve, transition to psychosis defined by CAARMS criteria	31	29	Resting, eyes closed	Current source density (μA/mm2)	Increased activity in the left medial frontal gyrus	↑	N/A
Tikka, Yadav et al. (2014)	Schizophrenia	ICD-10 DRC	Drug naïve, first episode not defined	37	30	Resting, eyes closed	Spectral power, left frontal, low gamma (30-50 Hz)	Increased spectral power compared with healthy controls	↑	0.602
Tikka, Yadav et al. (2014)	Schizophrenia	ICD-10 DRC	Drug naïve, first episode not defined	37	30	Resting, eyes closed	Spectral power, left parietal, low gamma (30-50 Hz)	Increased spectral power compared with healthy controls	↑	0.480
Yeragani, Cashmere et al. (2006)	Schizophrenia (n=8), schizoaffective disorder (n=2)	Structured Clinical Interview for DSM-IV	Drug naïve, first episode not defined	8	8	Resting	Spontaneous spectral power of C4	Decreased spectral power compared with healthy controls (non-significant)	↓	-0.483
Yeragani, Cashmere et al. (2006)	Schizophrenia (n=8), schizoaffective disorder (n=2)	Structured Clinical Interview for DSM-IV	Drug naïve, first episode not defined	8	8	Resting	Spontaneous spectral power of F4	Decreased spectral power compared with healthy controls (non-significant)	↓	-0.506
Yeragani, Cashmere et al. (2006)	Schizophrenia (n=8), schizoaffective disorder (n=2)	Structured Clinical Interview for DSM-IV	Drug naïve, first episode not defined	8	8	Resting	Mean coherence between C4 and F4	Decreased coherence compared with healthy controls	↓	-1.430
Yeragani, Cashmere et al. (2006)	Schizophrenia (n=8), schizoaffective disorder (n=2)	Structured Clinical Interview for DSM-IV	Drug naïve, first episode not defined	8	8	Resting	Mean phase (degrees) between C4 and F4	Decreased coherence compared with healthy controls (non-significant)	↓	-0.126

Study	Diagnosis	Diagnostic Tool	Definition of first episode	Patient Number	Control Number	Task	Measurement of Gamma Oscillations	Summary of findings	Direction of difference, compared with controls	Hedge's g
Flynn, Alexander et al. (2008)	Schizophrenia (n=32), schizophreniform disorder (12), psychosis not otherwise specified (n=4), schizoaffective bipolar type (n=2), schizoaffective depressive type (n=1), bipolar, manic (n=1), bipolar depressive (n=1), major depression with psychotic features (n=1), substance induced psychosis (n=1)	Structured Clinical Interview for DSM-IV	First contact with a mental health service, 50 receiving antipsychotics	55	110	Auditory oddball	Phase synchrony	Increased gamma phase synchrony compared with healthy controls	↑	N/A
Gallinat, Winterer et al. (2004)	Schizophrenia	Structured Clinical Interview for DSM-IV	10 patients drug naive first episode, 5 were medication free for four weeks	15	15	Auditory oddball	Early evoked response (20-100ms)	No difference in evoked gamma response compared with healthy controls.	–	N/A
Gallinat, Winterer et al. (2004)	Schizophrenia	Structured Clinical Interview for DSM-IV	10 patients drug naive first episode, 5 were medication free for four weeks	15	15	Auditory oddball	Late evoked response (220-350ms)	No difference in evoked gamma response compared with healthy controls overall, decreased evoked gamma response in patients over right frontal region only.	–	N/A
Slewa-Younan, Gordon et al. (2004)	Schizophrenia	Composite International Diagnostic Interview	First presentation to health services with psychotic symptoms, receiving antipsychotics	24	24	Auditory oddball	Early gamma phase synchrony (circular variance)	Decreased gamma phase synchrony compared with healthy controls	↓	N/A
Slewa-Younan, Gordon et al. (2004)	Schizophrenia	Composite International Diagnostic Interview	First presentation to health services with psychotic symptoms, receiving antipsychotics	24	24	Auditory oddball	Magnitude of early phase gamma synchrony	Decreased gamma magnitude in left and right hemispheres compared with healthy controls	↓	N/A
Slewa-Younan, Gordon et al. (2004)	Schizophrenia	Composite International Diagnostic Interview	First presentation to health services with psychotic symptoms, receiving antipsychotics	24	24	Auditory oddball	Latency of early gamma phase synchrony (msec)	Increased latency of frontal synchrony relative to posterior synchrony compared with healthy controls	↑	N/A
Symond, Harris et al. (2005)	Schizophrenia	Semistructured interview, based on ICD-10 and DSM-IV criteria	First episode not defined, 36 receiving antipsychotic medication	40	40	Auditory oddball	Global synchrony - magnitude (standarized circular variance index) (early gamma)	Lower magnitude of global early gamma compared with healthy controls	↓	-0.875
Symond, Harris et al. (2005)	Schizophrenia	Semistructured interview, based on ICD-10 and DSM-IV criteria	First episode not defined, 36 receiving antipsychotic medication	40	40	Auditory oddball	Global synchrony - magnitude (standarized circular variance index) (late gamma)	Lower magnitude of global late gamma compared with healthy controls (non-significant)	↓	-0.140
Symond, Harris et al. (2005)	Schizophrenia	Semistructured interview, based on ICD-10 and DSM-IV criteria	First episode not defined, 36 receiving antipsychotic medication	40	40	Auditory oddball	Global synchrony - Latency (msec) (early gamma)	Increased latency of global early gamma compared with healthy controls	↑	0.408
Symond, Harris et al. (2005)	Schizophrenia	Semistructured interview, based on ICD-10 and DSM-IV criteria	First episode not defined, 36 receiving antipsychotic medication	40	40	Auditory oddball	Global synchrony - Latency (msec) (late gamma)	Increased latency of global late gamma compared with healthy controls (non-significant)	↑	0.174
Taylor, McCarley et al. (2013)	Schizophrenia (n=18), schizoaffective (n=8), schizophreniform (n=1), delusional disorder (n=1)	Structured Clinical Interview for DSM-IV	Within a year of first hospitalisation, receiving antipsychotics	28	44	Auditory oddball	Evoked power (at Fz)	Decreased evoked gamma power compared with healthy controls	↓	-0.493

Study	Diagnosis	Diagnostic Tool	Definition of first episode	Patient Number	Control Number	Task	Measurement of Gamma Oscillations	Summary of findings	Direction of difference, compared with controls	Hedge's g
Taylor, McCarley et al. (2013)	Schizophrenia (n=18), schizoaffective (n=8), schizophreniform (n=1), delusional disorder (n=1)	Structured Clinical Interview for DSM-IV	Within a year of first hospitalisation, receiving antipsychotics	28	44	Auditory oddball	Evoked Power (at Cz)	Decreased evoked gamma power compared with healthy controls	↓	-0.450
Taylor, McCarley et al. (2013)	Schizophrenia (n=18), schizoaffective (n=8), schizophreniform (n=1), delusional disorder (n=1)	Structured Clinical Interview for DSM-IV	Within a year of first hospitalisation, receiving antipsychotics	28	44	Auditory oddball	Intertrial phase locking (at Fz)	Decreased intertrial phase locking compared with healthy controls	↓	-0.603
Taylor, McCarley et al. (2013)	Schizophrenia (n=18), schizoaffective (n=8), schizophreniform (n=1), delusional disorder (n=1)	Structured Clinical Interview for DSM-IV	Within a year of first hospitalisation, receiving antipsychotics	28	44	Auditory oddball	Intertrial phase locking (at Cz)	Decreased intertrial phase locking compared with healthy controls	↓	-0.429
Williams, Whitford et al. (2009a)	Schizophrenia	Structured Clinical Interview for DSM-IV	Within 3 months of presentation to mental health services, receiving antipsychotics	25	23	Auditory oddball	Early gamma synchrony (circular variance)	Decreased early gamma synchrony compared with healthy controls	↓	-0.685
Williams, Whitford et al. (2009a)	Schizophrenia	Structured Clinical Interview for DSM-IV	Within 3 months of presentation to mental health services, receiving antipsychotics	25	23	Auditory oddball	Late gamma synchrony (circular variance)	Decreased late gamma synchrony compared with healthy controls	↓	-0.604
Spencer, Salisbury et al. (2008)	Schizophrenia	Structured Clinical Interview for DSM-IV	First hospitalisation, receiving antipsychotics	16	33	Auditory steady state responses	Evoked power (μV^2)	Decreased evoked gamma power compared with healthy controls	↓	N/A
Spencer, Salisbury et al. (2008)	Schizophrenia	Structured Clinical Interview for DSM-IV	First hospitalisation, receiving antipsychotics	16	33	Auditory steady state responses	Phase locking factor	Decreased phase locking compared with healthy controls	↓	N/A
Spencer, Salisbury et al. (2008)	Bipolar affective disorder with psychotic symptoms (n=13), major depression with psychotic symptoms (n=3)	Structured Clinical Interview for DSM-IV	First hospitalisation, receiving antipsychotics	16	33	Auditory steady state responses	Evoked power (μV^2)	Decreased evoked gamma power compared with healthy controls	↓	-0.598
Spencer, Salisbury et al. (2008)	Bipolar affective disorder with psychotic symptoms (n=13), major depression with psychotic symptoms (n=3)	Structured Clinical Interview for DSM-IV	First hospitalisation, receiving antipsychotics	16	33	Auditory steady state responses	Phase locking factor	Decreased phase locking compared with healthy controls	↓	-0.603
Tada, Nagai et al. (2014)	Schizophrenia	DSM-IV	Continuous psychotic symptoms within the past 24 months, without previously demonstrating psychotic symptoms, receiving antipsychotics	13	21	Auditory steady state responses	Event related spectral perturbation at 200-300ms	Decreased event-related spectral perturbation compared with healthy controls	↓	-1.039
Tada, Nagai et al. (2014)	Schizophrenia	DSM-IV	Continuous psychotic symptoms within the past 24 months, without previously demonstrating psychotic symptoms, receiving antipsychotics	13	21	Auditory steady state responses	Event related spectral perturbation at 300-400ms	Decreased event-related spectral perturbation compared with healthy controls	↓	-1.107
Tada, Nagai et al. (2014)	Schizophrenia	DSM-IV	Continuous psychotic symptoms within the past 24 months, without previously demonstrating psychotic symptoms,	13	21	Auditory steady state responses	Event related spectral perturbation at 400-500ms	Decreased event-related spectral perturbation compared with healthy controls	↓	-0.944

Study	Diagnosis	Diagnostic Tool	Definition of first episode	Patient Number	Control Number	Task	Measurement of Gamma Oscillations	Summary of findings	Direction of difference, compared with controls	Hedge's g
			receiving antipsychotics							
Tada, Nagai et al. (2014)	Schizophrenia	DSM-IV	Continuous psychotic symptoms within the past 24 months, without previously demonstrating psychotic symptoms, receiving antipsychotics	13	21	Auditory steady state responses	Intertrial phase coherence at 200-300ms	Decreased intertrial phase coherence compared with healthy controls	↓	-0.783
Tada, Nagai et al. (2014)	Schizophrenia	DSM-IV	Continuous psychotic symptoms within the past 24 months, without previously demonstrating psychotic symptoms, receiving antipsychotics	13	21	Auditory steady state responses	Intertrial phase coherence at 300-400ms	Decreased intertrial phase coherence compared with healthy controls	↓	-0.844
Tada, Nagai et al. (2014)	Schizophrenia	DSM-IV	Continuous psychotic symptoms within the past 24 months, without previously demonstrating psychotic symptoms, receiving antipsychotics	13	21	Auditory steady state responses	Intertrial phase coherence at 400-500ms	Decreased intertrial phase coherence compared with healthy controls	↓	-0.783
Leicht, Andreou et al. (2015)	Schizophrenia	Mini International Neuropsychiatric Interview	First diagnosis and treatment less than a year prior to study participation, 19 receiving antipsychotics	21	21	Auditory reaction task	Evoked power (μV^2) (easy condition)	Decreased evoked gamma power compared with healthy controls (non-significant)	↓	-0.3
Leicht, Andreou et al. (2015)	Schizophrenia	Mini International Neuropsychiatric Interview	First diagnosis and treatment less than a year prior to study participation, 19 receiving antipsychotics	21	21	Auditory reaction task	Evoked power (μV^2) (difficult condition)	Decreased evoked gamma power compared with healthy controls	↓	-0.666
Leicht, Andreou et al. (2015)	Schizophrenia	Mini International Neuropsychiatric Interview	First diagnosis and treatment less than a year prior to study participation, 19 receiving antipsychotics	21	21	Auditory reaction task	Phase locking factor (easy condition)	Decreased phase locking factor compared with healthy controls (non-significant)	↓	-0.261
Leicht, Andreou et al. (2015)	Schizophrenia	Mini International Neuropsychiatric Interview	First diagnosis and treatment less than a year prior to study participation, 19 receiving antipsychotics	21	21	Auditory reaction task	Phase locking factor (difficult condition)	Decreased phase locking factor compared with healthy controls	↓	-0.654
Minzenberg, Firl et al. (2010)	Schizophrenia	Structured Clinical Interview for DSM-IV TR or Kiddie-SADS-Present and Lifetime Version, if under 18 years	Onset of psychosis less than a year prior to study participation, 32 receiving antipsychotics	53	29	Cognitive task - preparing to overcome prepotency	Induced power (frontal)	Decreased gamma power compared with healthy controls	↓	-0.782
Williams, Whitford et al. (2009b)	Schizophrenia	Structured Clinical Interview for DSM-IV	First contact with a mental health service with psychotic symptoms, recruited within 8 months of presentation, 26 receiving antipsychotics	28	72	Facial emotion perception	Absolute gamma synchrony (inverse circular variance) at left temporal region	Increased absolute gamma synchrony, compared with healthy controls.	↑	0.75

Table 3. Gamma Oscillations in Clinical High Risk

Study	Definition of risk	At Risk Number	Control Number	Task	Measurement of gamma oscillations	Summary of findings	Direction of difference, compared with controls	Hedge's g
Andreou, Leicht et al. (2015)	Early Detection and Intervention program of the German Research Network on Schizophrenia Criteria	28	23	Resting state, eyes closed	Spontaneous power	No difference in spectral power between groups	–	N/A
Andreou, Leicht et al. (2015)	Early Detection and Intervention program of the German Research Network on Schizophrenia Criteria	28	23	Resting state, eyes closed	Resting connectivity	No difference in connectivity between groups	–	N/A
Leicht, Vauth et al. (2016)	Early Detection and Intervention program of the German Research Network on Schizophrenia Criteria	27	26	Auditory reaction task	Latency of peak gamma band response (ms)	No difference in gamma peak latency between groups	–	-0.014
Leicht, Vauth et al. (2016)	Early Detection and Intervention program of the German Research Network on Schizophrenia Criteria	27	26	Auditory reaction task	Evoked spectral power (μV^2)	Decreased spectral power compared with healthy controls	↓	-0.501
Leicht, Vauth et al. (2016)	Early Detection and Intervention program of the German Research Network on Schizophrenia Criteria	27	26	Auditory reaction task	Phase locking factor	Decreased phase locking factor compared with healthy controls (non-significant)	↓	-0.398
Leicht, Vauth et al. (2016)	Early Detection and Intervention program of the German Research Network on Schizophrenia Criteria	27	26	Auditory reaction task	Peak frequency (Hz)	Decreased peak frequency compared with healthy controls	↓	-0.149
Perez, Roach et al. (2013)	Criteria for Prodromal Syndrome	43	42	Auditory oddball task	Evoked spectral power	Decreased evoked power compared with healthy controls	↓	-0.559
Perez, Roach et al. (2013)	Criteria for Prodromal Syndrome	43	42	Auditory oddball task	Total power	Decreased total power compared with healthy controls (non-significant)	↓	-0.087
Perez, Roach et al. (2013)	Criteria for Prodromal Syndrome	43	42	Auditory oddball task	Phase locking factor	Decreased phase locking factor compared with healthy controls (trend level significance)	↓	-0.415
Ramyead, Kometer et al. (2015)	Basel Screening Instrument for Psychosis (based on PACE criteria). ARMS-T (n=23), ARMS-NT (n=40)	63	29	Resting state, eyes closed	Current source density (μA/mm2)	Source frontal activity progressively increased from HC to ARMS-NT to ARMS-T. ARMS-T increased gamma activity in mPFC bilaterally	↑	N/A
Ramyead, Kometer et al. (2015)	Basel Screening Instrument for Psychosis (based on PACE criteria). ARMS-T (n=23), ARMS-NT (n=40)	63	29	Resting state, eyes closed	Lagged phase synchronisation	Stronger decreasing lagged phase synchronicity with increasing Euclidian distance in ARMS-T than ARMS-NT and healthy controls	NR	N/A
Ramyead, Kometer et al. (2015)	Basel Screening Instrument for Psychosis (based on PACE criteria). ARMS-T (n=23), ARMS-NT (n=40)	63	29	Resting state, eyes closed	Spontaneous spectral power (μV)	ARMS-T showed increased gamma power in medial prefrontal cortex compared with healthy controls	↑	N/A
Ramyead, Studerus et al. (2015)	Basel Screening Instrument for Psychosis (based on PACE criteria). ARMS-T (n=18), ARMS-NT (n=35)	53	N/A	Resting state, eyes closed	Machine learning of current source density and lagged phase synchronisation across frequency bands	Three highest gamma band contributors to prediction were the left inferior parietal lobule, precuneus and the right posterior temporal cortex	NR	N/A

Study	Definition of risk	At Risk Number	Control Number	Task	Measurement of gamma oscillations	Summary of findings	Direction of difference, compared with controls	Hedge's g
Tada, Nagai et al. (2014)	Structured Interview for Prodromal Symptoms	15	21	Auditory steady state response	Intertrial phase coherence at 400-500ms	Decreased intertrial phase coherence compared with healthy controls	↓	N/A
Tada, Nagai et al. (2014)	Structured Interview for Prodromal Symptoms	15	21	Auditory steady state response	Event related spectral perturbation	Decreased event-related spectral perturbation compared with healthy controls	↓	N/A
Tada, Nagai et al. (2014)	Structured Interview for Prodromal Symptoms	15	21	Auditory steady state response	Intertrial phase coherence at 300-400ms	Decreased intertrial phase coherence compared with healthy controls	↓	N/A

Table 4. Gamma Oscillations in Familial High Risk

Study	Definition of risk	At Risk Number	Control Number	Task	Measurement of gamma oscillations	Summary of findings	Direction of difference	Hedge's g
Bandyopadhyaya, Nizamie et al. (2011)	First degree relatives of schizophrenia patients, with no psychiatric disorder	20	20	Resting state	Spontaneous power spectral density	Increased left temporal spontaneous power in relatives compared with healthy controls	↑	N/A
Bandyopadhyaya, Nizamie et al. (2011)	First degree relatives of schizophrenia patients, with no psychiatric disorder	20	20	Resting state	Coherence (Inter H Frontal)	Decreased coherence in relatives compared with healthy controls	↓	-0.91
Bandyopadhyaya, Nizamie et al. (2011)	First degree relatives of schizophrenia patients, with no psychiatric disorder	20	20	Resting state	Coherence (Inter H Parietal)	Decreased coherence in relatives compared with healthy controls	↓	-0.929
Bandyopadhyaya, Nizamie et al. (2011)	First degree relatives of schizophrenia patients, with no psychiatric disorder	20	20	Resting state	Coherence (Inter H Temporal)	Decreased coherence in relatives compared with healthy controls	↓	-0.728
Diez, Suazo et al. (2013)	First degree relatives of schizophrenia with no Axis I psychiatric disorder and who had not received psychiatric treatment	23	27	Auditory oddball task	Noise power value at O1 (μV^2)	No difference in gamma noise magnitude between first degree relatives and healthy controls.	–	N/A
Diez, Suazo et al. (2014)	First degree relatives of schizophrenia patients, with no psychiatric disorder	24	27	Auditory oddball task	Total spectral power at T5 (μV^2)	No difference in gamma spectral power between relatives and controls. Inverse association of gamma power with verbal and working memory	–	-0.105
Donkers, Schwikert et al. (2011)	Adolescent first degree relatives of schizophrenia or schizoaffective disorder patients	24	30	Visual oddball task	Phase locking factor, evoked power and total power	Methods state phase locking factor, evoked power or total power compared between relatives and controls in the gamma band. However, group means and statistical tests not reported for gamma - only delta, theta and alpha.	NR	N/A
Hall, Taylor et al. (2011a)	Monozygotic well co-twins whose twin has a diagnosis of schizophrenia	9	147	Auditory oddball task	Evoked spectral power ($\mu V2$)	Decreased spectral power of unaffected identical co-twins compared with controls	↓	-0.520
Hall, Taylor et al. (2011a)	Monozygotic well co-twins whose twin has a diagnosis of schizophrenia	9	147	Auditory oddball task	Phase locking factor	Decreased phase locking factor of unaffected identical co-twins compared with controls (non-significant)	↓	-0.460
Hall, Taylor et al. (2011b)	Relatives of schizophrenia or schizoaffective disorder patients who did not have a lifetime diagnosis of psychotic disorder, bipolar disorder, or a schizophrenia spectrum personality disorder	25	34	Paired auditory clicks	Evoked spectral power to paired stimuli	No statistical difference in evoked spectral power between relatives and healthy controls for either stimuli 1, stimuli 2, or the subtraction of these	–	N/A
Hong, Summerfelt et al. (2004)	First degree relatives with schizophrenia spectrum personality traits	11	17	Auditory steady state response	Evoked spectral power (μV^2)	Decreased spectral power in first degree relatives with schizophrenia spectrum personality symptoms compared with healthy controls	↓	N/A
Hong, Summerfelt et al. (2012)	First degree relatives of schizophrenia patients, without schizophrenia	80	110	Resting state, eyes closed	Single trial spontaneous power spectrum density, low gamma (20-40 Hz)	No difference in gamma power spectrum density between relatives and controls	–	N/A
Hong, Summerfelt et al. (2012)	First degree relatives of schizophrenia patients, without schizophrenia	80	110	Resting state, eyes closed	Single trial spontaneous power spectrum density, gamma (40-85 Hz)	No difference in gamma power spectrum density between relatives and controls	–	-0.170
Hong, Summerfelt et al. (2012)	First degree relatives of schizophrenia patients, without schizophrenia	80	110	Resting state, eyes closed	Single trial spontaneous power spectrum density, high gamma (>85Hz)	Not reported but similar results to (40-85Hz)	–	N/A
Hong, Summerfelt et al. (2012)	First degree relatives of schizophrenia patients, without schizophrenia	80	110	Paired auditory clicks	Single trial power spectrum density, low gamma (20-40 Hz)	No difference in gamma power spectrum density between relatives and controls	–	N/A
Hong, Summerfelt et al. (2012)	First degree relatives of schizophrenia patients, without schizophrenia	80	110	Paired auditory clicks	Single trial power spectrum density, gamma (40-85 Hz)	No difference in gamma power spectrum density between any groups	–	N/A
Leicht, Karch et al. (2011)	Siblings of patients with schizophrenia, with no lifetime history of psychotic disorder	17	17	Auditory reaction task	Phase locking factor	Decreased phase locking factor of unaffected siblings compared with controls	↓	-1.079

Study	Definition of risk	At Risk Number	Control Number	Task	Measurement of gamma oscillations	Summary of findings	Direction of difference	Hedge's g
Leicht, Karch et al. (2011)	Siblings of patients with schizophrenia, with no lifetime history of psychotic disorder	17	17	Auditory reaction task	Evoked spectral power (μV)	Decreased spectral power of unaffected siblings compared with healthy controls	↓	-1.135
Rass, Forsyth et al. (2012)	First degree relatives of schizophrenia patients	35	56	Auditory steady state response	Mean trial power (change from baseline)	Decreased meant trial power in relatives compared with healthy controls.	↓	-0.733
Rass, Forsyth et al. (2012)	First degree relatives of schizophrenia patients	35	56	Auditory steady state response	Phase locking factor	Decreased phase locking factor in relatives compared with healthy controls. No significant group effect (F statistic and p value not reported).	↓	N/A
Tikka, Nizamie et al. (2015)	First degree relatives of schizophrenia patients	30	30	Resting state, eyes closed	Right temporal spontaneous spectral power in the 30-50Hz band	Spectral power in the right temporal region significantly higher in relatives compared with healthy controls.	↑	N/A
Tikka, Nizamie et al. (2015)	First degree relatives of schizophrenia patients	30	30	Resting state, eyes closed	Right parietal spontaneous spectral power in the 50-70Hz band	Spectral power in the right parietal higher in relatives compared with healthy controls.	↑	N/A
Tikka, Nizamie et al. (2015)	First degree relatives of schizophrenia patients	30	30	Resting state, eyes closed	Right temporal spontaneous spectral power in the 50-70Hz band	Spectral power in the right temporal significantly higher in relatives compared with healthy controls.	↑	N/A
Tikka, Nizamie et al. (2015)	First degree relatives of schizophrenia patients	30	30	Resting state, eyes closed	Right parietal spontaneous spectral power in the 70-100Hz band	Spectral power in the right parietal higher in relatives compared with healthy controls	↑	N/A
Tikka, Nizamie et al. (2015)	First degree relatives of schizophrenia patients	30	30	Resting state, eyes closed	Right temporal spontaneous spectral power in the 70-100Hz band	Spectral power in the right temporal significantly higher in relatives compared with healthy controls	↑	N/A
Tikka, Nizamie et al. (2015)	First degree relatives of schizophrenia patients	30	30	Resting state, eyes closed	Inter hemispheric cross spectral coherence	No statistically significant differences in inter- or intra-hemispheric coherence between relatives and healthy controls	–	N/A
Venables, Bernat et al. (2009)	First degree relatives of schizophrenia patients	61	79	Resting state, eyes open	Spontaneous power (μV^2)	Increased power at anterior and temporal sites in relatives compared with controls.	↑	N/A
Winterer, Egan et al. (2001)	Siblings of patients with schizophrenia, with no lifetime history of psychotic disorder	166	58	Resting state, eyes closed	Spontaneous power (μV)	No difference between groups, however means, F statistics and p values not reported	–	N/A
Winterer, Egan et al. (2001)	Siblings of patients with schizophrenia, with no lifetime history of psychotic disorder	166	58	Resting state, eyes closed	Inter-hemispheric power coherence	No difference between groups, however means, F statistics and p values not reported	–	N/A
Winterer, Egan et al. (2001)	Siblings of patients with schizophrenia, with no lifetime history of psychotic disorder	166	58	Resting state, eyes closed	Intra-hemispheric power coherence	No difference between groups, however means, F statistics and p values not reported	–	N/A
Winterer, Coppola et al. (2004)	Unaffected siblings of patients with schizophrenia	115	89	Auditory oddball task	Frontal noise power	Increased frontal noise power in unaffected siblings compared with healthy controls	↑	0.277

Table 5. Gamma Oscillations in Schizotypy

Study	Definition of schizotypy	High schizotypy Number	Healthy control / low schizotypy Number	Task	Measurement of gamma	Summary of findings	Direction of difference	Hedge's g
Brenner, Sporns et al. (2003)	Schizotypal personality disorder (diagnostic instrument not defined)	11	22	Auditory steady state response	Evoked power (μV^2)	No difference in power between schizotypal personality disorder and non-psychiatric controls.	–	N/A
Fuggetta, Bennett et al. (2014)	Grouped into high and low schizotypy groups based on answers to Unusual Experiences and Cognitive Disorganisation sub scales of the Oxford-Liverpool Inventory of Feelings and Experiences	16	16	Resting state, eyes closed	Relative spectral power (%)	Decreased spectral power in high schizotypy individuals compared with low schizotypy individuals (non-significant)	↓	-0.416
Kornmayer, Leicht et al. (2015)	Healthy volunteers who completed the Schizotypal Personality Questionnaire	24	N/A	Visual reaction task with physically salient distracter	Evoked spectral power (μV^2)	Early evoked visual gamma spectral power positively correlated with positive schizotypal personality traits	↑	1.404
Koychev, Deakin et al. (2011)	Grouped into high and low schizotypy groups based on answers to the short version of the Schizotypal Personality Questionnaire	18	20	Visual working memory task	Phase locking factor	Decreased phase locking factor in high schizotypy individuals compared with low schizotypy individuals	↓	-0.678
Koychev, Deakin et al. (2011)	Grouped into high and low schizotypy groups based on answers to the short version of the Schizotypal Personality Questionnaire	18	20	Visual working memory task	Evoked spectral power (μV)	Increased spectral power in high schizotypy individuals compared with low schizotypy individuals	↑	0.719
Skosnik, Krishnan et al. (2006)	Schizotypal personality questionnaire	17	N/A	Auditory steady state response	Evoked Log_{10} Spectral power (μV^2) at Fz	Negative correlation of schizotypal scores with power at 20Hz in cannabis users. No correlation within non-cannabis using group or at other frequencies.	↓	N/A
Tcheslavski (2008)	Grouped into high and low schizotypy groups based on answers to the short version of the Schizotypal Personality Questionnaire	20	19	Resting state, eyes closed	Average spectral power	Increased gamma average spectral power in high schizotypy compared with low schizotypy, most pronounced in fronto-central region.	↑	N/A
Tcheslavski and Beex (2010)	Grouped into high and low schizotypy groups based on answers to the short version of the Schizotypal Personality Questionnaire	20	20	Resting state, eyes closed	Average phase synchrony	Reported increased phase synchrony in high schizotypy smokers compared with low schizotypy smokers, as well as high schizotypy non-smokers compared with low schizotypy non-smokers. For all electrode pairs expect C3-F3. However, no mean values, F statistics or p values reported.	↑	N/A
Vernon, Haenschel et al. (2005)	Healthy volunteers (n=40), separated into high/low unreality groups based on Personality Schizotypy Questionnaire scores	NR	NR	Auditory habituation task	Induced spectral power (μV)	Decreased spectral power in individuals with high unreality schizotypy scores compared with individuals with low unreality scores (non-significant)	↓	N/A

Table 6. Assessment of Bias

Study	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Exposure 1	Exposure 2	Exposure 3
Andreou, Leicht et al. (2015)	1	0	1	1	2	0	1	1
Andreou, Nolte et al. (2015)	1	0	1	1	1	0	1	1
Bandyopadhyaya, Nizamie et al. (2011)	1	0	0	1	2	0	1	1
Brenner, Sporns et al. (2003)	0	0	1	0	0	0	1	1
Diez, Suazo et al. (2013)	1	0	1	1	0	0	1	1
Diez, Suazo et al. (2014)	0	0	1	1	1	0	1	1
Donkers, Schwikert et al. (2011)	1	0	1	1	2	0	1	0
Flynn, Alexander et al. (2008)	1	0	0	1	0	0	1	1
Fuggetta, Bennett et al. (2014)	1	0	1	1	2	0	1	1
Gallinat, Winterer et al. (2004)	1	0	1	1	2	0	1	1
Garakh, Zaytseva et al. (2015)	1	1	0	0	2	0	1	1
Hall, Taylor et al. (2011a)	1	0	0	1	0	0	1	1
Hall, Taylor et al. (2011b)	1	0	0	1	0	1	1	1
Hong, Summerfelt et al. (2004)	0	0	1	1	2	0	1	1
Hong, Summerfelt et al. (2012)	1	0	1	1	2	0	1	1
Kikuchi, Koenig et al. (2007)	1	0	0	1	2	0	1	1
Kikuchi, Hashimoto et al. (2011)	1	0	0	1	2	0	1	1
Kornmayer, Leicht et al. (2015)	1	0	N/A	N/A	N/A	N/A	N/A	N/A
Koychev, Deakin et al. (2011)	1	0	1	1	2	0	1	1
Leicht, Karch et al. (2011)	1	0	1	1	0	0	1	1
Leicht, Vauth et al. (2016)	1	1	0	1	2	0	1	1
Leicht, Andreou et al. (2015)	1	0	1	1	2	0	1	1
Minzenberg, Firl et al. (2010)	1	0	1	1	0	0	1	0
Perez, Roach et al. (2013)	1	0	1	1	2	0	1	1
Ramyead, Kometer et al. (2015)	1	1	0	1	0	0	1	1
Ramyead, Studerus et al. (2015)	1	1	N/A	N/A	N/A	N/A	N/A	N/A
Ramyead, Studerus et al. (2016)	1	1	1	1	0	0	1	1
Rass, Forsyth et al. (2012)	1	0	1	1	1	0	1	1
Skosnik, Krishnan et al. (2006)	1	0	N/A	N/A	N/A	N/A	N/A	N/A
Slewa-Younan, Gordon et al. (2004)	1	0	0	1	1	0	1	1
Spencer, Salisbury et al. (2008)	1	0	1	1	2	0	1	0
Symond, Harris et al. (2005)	1	0	0	0	2	0	1	1

Study	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Exposure 1	Exposure 2	Exposure 3
Tada, Nagai et al. (2014)	1	0	0	1	2	0	1	1
Taylor, McCarley et al. (2013)	1	0	1	1	2	0	1	1
Tcheslavski (2008)	1	0	1	1	1	0	1	1
Tcheslavski and Beex (2010)	1	0	1	1	1	0	1	1
Tikka, Yadav et al. (2014)	1	0	0	0	2	1	1	0
Tikka, Nizamie et al. (2015)	1	0	0	1	1	1	1	1
Venables, Bernat et al. (2009)	1	0	1	1	2	0	1	0
Vernon, Haenschel et al. (2005)	1	0	1	1	0	0	1	1
Williams, Whitford et al. (2009a)	1	0	0	1	2	0	1	1
Williams, Whitford et al. (2009b)	1	0	0	1	2	0	1	1
Winterer, Egan et al. (2001)	1	0	1	1	0	1	1	1
Winterer, Coppola et al. (2004)	1	0	1	1	0	1	1	1
Yeragani, Cashmere et al. (2006)	1	1	1	0	1	1	1	1

Table 7. Assessment of Gamma Artefact Correction

Study	Powerline Noise	EMG Artefact	Saccadic Muscle Artefact	Scores
Andreou, Leicht et al. (2015)	Electrically shielded	ICA	ICA	3
Andreou, Nolte et al. (2015)	Electrically shielded	ICA	ICA	3
Bandyopadhyaya, Nizamie et al. (2011)	Not addressed	Instructed to relax	Not addressed	0
Brenner, Sporns et al. (2003)	Not addressed	Manually removed	Manually removed	0
Diez, Suazo et al. (2013)	Not addressed	Manually removed	Manually removed	0
Diez, Suazo et al. (2014)	Not addressed	Manually removed	Manually removed	0
Donkers, Schwikert et al. (2011)	Notch filter	Not addressed	Not addressed	1
Flynn, Alexander et al. (2008)	Not addressed	Not addressed	Not addressed	0
Fuggetta, Bennett et al. (2014)	Notch filter	Instructed to relax	Not addressed	1
Gallinat, Winterer et al. (2004)	Electrically shielded and notch filter	Manually removed	Manually removed	1
Garakh, Zaytseva et al. (2015)	Not addressed	Automated removal	Automated removal	2
Hall, Taylor et al. (2011a)	Not addressed	Manually removed	Manually removed	0
Hall, Taylor et al. (2011b)	Not addressed	Manually removed	Manually removed	0
Hong, Summerfelt et al. (2004)	Not addressed	Instructed to relax	Manually removed	0
Hong, Summerfelt et al. (2012)	Not addressed	Not addressed	Automated removal	1
Kikuchi, Koenig et al. (2007)	Not addressed	Instructed to relax, artefact manually removed	Manually removed	0
Kikuchi, Hashimoto et al. (2011)	Not addressed	Instructed to relax, artefact manually removed	Manually removed	0
Kornmayer, Leicht et al. (2015)	Electrically shielded	ICA and algorithm based on power spectrum	ICA and algorithm based on power spectrum	3
Koychev, Deakin et al. (2011)	Not addressed	Not addressed	Not addressed	1
Leicht, Karch et al. (2011)	Electrically shielded	Not addressed	Not addressed	1
Leicht, Vauth et al. (2016)	Active electrodes, notch filter	ICA	ICA	3
Leicht, Andreou et al. (2015)	Electrically shielded, active electrodes	Manually removed	Manually removed	1
Minzenberg, Firl et al. (2010)	Electrically shielded	ICA	ICA	3
Perez, Roach et al. (2013)	Not addressed	Not addressed	Not addressed	0
Ramyead, Kometer et al. (2015)	Not addressed	ICA	ICA	2
Ramyead, Studerus et al. (2015)	Not addressed	ICA	ICA	2
Ramyead, Studerus et al. (2016)	Not addressed	ICA	ICA	2
Rass, Forsyth et al. (2012)	Not addressed	Not addressed	Not addressed	0
Skosnik, Krishnan et al. (2006)	Not addressed	Not addressed	Not addressed	0
Slewa-Younan, Gordon et al. (2004)	Notch filter	Not addressed	Not addressed	1
Spencer, Salisbury et al. (2008)	Not addressed	Not addressed	Not addressed	0
Symond, Harris et al. (2005)	Not addressed	Not addressed	Not addressed	0
Tada, Nagai et al. (2014)	Electrically shielded, notch filter	Not addressed	Not addressed	1
Taylor, McCarley et al. (2013)	Not addressed	Not addressed	Not addressed	0

Study	Powerline Noise	EMG Artefact	Saccadic Muscle Artefact	Scores
Tcheslavski (2008)	Not addressed	Not addressed	Not addressed	0
Tcheslavski and Beex (2010)	Not addressed	Not addressed	Not addressed	0
Tikka, Yadav et al. (2014)	Not addressed	Manually removed	Manually removed	0
Tikka, Nizamie et al. (2015)	Not addressed	Manually removed	Manually removed	0
Venables, Bernat et al. (2009)	Not addressed	Not addressed	Not addressed	0
Vernon, Haenschel et al. (2005)	Not addressed	Manually removed	Manually removed	0
Williams, Whitford et al. (2009a)	Notch filter	Not addressed	Not addressed	1
Williams, Whitford et al. (2009b)	Not addressed	Not addressed	Not addressed	0
Winterer, Egan et al. (2001)	Not addressed	Manually removed	Manually removed	0
Winterer, Coppola et al. (2004)	Not addressed	Manually removed	Manually removed	0
Yeragani, Cashmere et al. (2006)	Notch filter	Not addressed	Not addressed	1